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EXAMINER	
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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,361	GOLZ ET AL.	
	Examiner	Art Unit	
	SHARON WEN	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *4,5,7 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/20/2008, has been entered.

Claims 12-26 have been canceled.

Claims 1-11 are currently pending.

Claims 4-5, 7 and 11 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Inventions/species, there being no allowable generic or linking claim.

Claims 1-3, 6 and 8-10 are currently under examination as they read on the a method of screening for therapeutic agents.

2. This Action will be in response to Applicant's Arguments/Remarks, filed 11/20/2008.

The rejections of record can be found in the previous Office Action, mailed 06/20/2008.

Specification

3. Applicant's amendment to the specification, filed 11/20/2008, has been entered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 6 and 8-10 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for screening a test compound for its ability to bind NPEPL1or regulate NPEPL1 activity, does not reasonably provide enablement for using any compound that has ability to bind NPEPL1or regulate NPEPL1 activity for the treatment of cardiovascular disease as the elected species of

disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant's argument has been considered but has not been found convincing essentially for reasons of record and reiterated herein for Applicant's convenience.

> The instant specification is enabled for a process for screening a compound that binds to NPEPL1 or regulates NPEPL1 activity (see page 29-36). However the specification as-filed does not provide sufficient enabling description for using any compounds that has ability to bind NPEPL1or regulate NPEPL1 activity to treat multitudes of disease broadly encompassed by the present claims, particularly, the elected species of cardiovascular diseases, atrial fibrillation.
>
> The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).
>
> With regards to the instant claims, their breadths, and the lack of guidance provided by the inventor, comprise the primary issues as regards the unpredictability of the claimed method.
>
> The instant claims are very broad, encompassing the use of multitude of compounds ability to bind NPEPL1or regulate NPEPL1 activity to treat diseases. The specification does not adequately teach how to effectively treat any disease with specific compound but only required the compound to exhibit ability to bind NPEPL1. However the claims do not specify any level of binding or regulating, i.e., inhibiting or enhancing NPEPL1 activity, thus the claims read on any measurable level of binding to regulation of NPEPL1.
>
> The instant specification provides a general discussion of administering antibody, inhibitors, or antagonists of NPEPL1 for therapeutic purposes (see Example 12 pages 86-87). However, the specification does not provide sufficient disclosure on how to use these therapeutic agents to treat any specific disease. Therefore, one of skill in the art would not be able to use any compound that binds NPEPL1 or regulates NPEPL1 activity to treat any disease as encompassed by the present claims.
>
> Furthermore, one of skill in the art is well aware that in vitro inhibition does not necessarily predict in vivo inhibition. The

specification does not teach how to extrapolate data obtained from various in vitro or in vivo experimental observations to the development of effective treatment for cardiovascular disease.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of *Ex parte Aggarwal*, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Also, it is noted that experimental protocols usually are conducted under defined conditions wherein the antagonist and the stimulus / insult occur at the same or nearly the same time. Protein targeting/inhibition is much easier to achieve under such controlled conditions than that experienced in human disorders such as cardiovascular disease.

For example, Kahan clearly states that no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2).

In view of the lack of established clinical protocols for effectively treating cardiovascular disease and in view of lack of sufficient working examples provided by Applicant of using any compounds that exhibit any level of binding to NPEPL1or regulating NPEPL1 activity, undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention and absent working examples providing evidence which is reasonably predictive that the claimed invention is effective for treating cardiovascular disease.

In response to Applicant's argument that Applicant only need to enable the claimed features of the invention and that the present claims are drawn to screening methods and do not recite treating a disease with compounds identified, the following is noted.

The grounds of rejection was set forth in view of the intended use in the preamble of the claims, i.e., "therapeutic agents useful in the treatment of the disease". The claims are broadly drawn to screening method for a therapeutic agent that binds NPEPL1 wherein said therapeutic agent is required to be useful in the treating of the various recited diseases. The newly added step of determining whether the test compound has an effect on a symptom of the disease in an in vivo assay does not enable the therapeutic agent to be useful for treatment of the disease because the specification, as-filed, does not provide any disclosure on how to use the therapeutic agent for treatment of any disease; nor does the specification disclosed what kind of effect the test compound has on any disease and the symptoms of the disease used to determine the effect. Furthermore, one of skill in the art would not know how to make all the therapeutic agents following the screening steps as claimed. Therefore, one of skill in the art would not know how to screen for a therapeutic agent that is useful in the treatment of the various recited diseases by simply performing the steps recited in the claims with a test compound that binds NPEPL1.

Given the breadth of the claims and the lack of disclosure on any specific diseases in which the therapeutic agent would be useful for treating, the present claims stand rejected for failing to meet the enablement requirement of 35 USC 112, first paragraph.

Applicant's argument has been considered in full but not found convincing.

Therefore, the rejection of record is **maintained** for the reasons of record, as it applies to the amended claims. The rejection of record is incorporated by reference herein, as if reiterated in full.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-3, 6, and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bandman et al. (US Patent 6,203,979 B1, see entire document).

Applicant's argument has been considered but has not been found convincing essentially for reasons of record and reiterated herein for Applicant's convenience.

> For the purposes of examination under prior art, the intended use for the test compound, i.e., "useful in the treatment of a disease" is not given patentable weight because such intended use does not distinguish from prior art.
>
> **Bandman et al. teach a method of screening for a compound that binds or regulates NPEPL1** (see entire document, in particular, see column 24, lines 52-65; column 28, lines 1-12; column 29, lines 10-20; and column 44, lines 28-67).
>
> As acknowledged by Applicant in the instant specification on page 4, Bandman et al. teach NPEPL1 as a human protease molecule (HUPM) as set forth by the amino acids 122-532 of SEQ ID NO: 12 of Patent '979. In particular, **the prior art teaches using purified NPEPL1 to screen for compounds that specifically binds NPEPL1 wherein the compound encompasses monoclonal or polyclonal antibodies** (see column 28, lines 1-12). Given that Bandman teach antibody as a screened test compound, one of ordinary skill in the art would have immediately envisaged the antibody regulating the activity of NPEPL1 because antibody, particularly polyclonal antibody, are known to have neutralizing capability.
>
> Furthermore, prior art also teach the step of contacting the test compound and NPEPL1 in a cell-free system such as ELISA (see column 24, lines 52-65) wherein one of ordinary skill in the art would have immediately envisage the antibody is coupled to a detectable label and the polypeptide is attached to a solid support. Furthermore, the prior art teaches a competitive binding assay which inherently teach antibody displacing a ligand (e.g., competitive antibody) which is first bound to the polypeptide (see column 24, line 60).
>
> As noted above, the present claims provide intended use for the test compound, i.e., for treating cardiovascular disease, however, such intended use does not distinguish from prior art.

In contrast to Applicant's argument that Bandman does not teach step (iii) of the present claims (i.e., "determining if the test compound has an effect on a symptom of the disease in an in vivo assay"), it is noted that Bandman implicitly taught the recited determining step (see column 26, lines 9-55) in the discussion of administering the antagonist of HUPM to a subject to treat various disorders, wherein antagonist of HUPM

reads on a test compound that binds NPEPL1 (see previous rejection above). Under the broadest reasonable interpretation, administering the antagonist of HUPM for treatment of diseases reads on determining if the test compound has an effect on a symptom of the disease in an in vivo assay because by administering the test compound for treating disease, one of ordinary skill in the art would recognized that the test compound would necessarily be determined whether it has an effect on any symptoms of the disease. It is also noted that in vivo assay broadly reads on administering in a subject.

Applicant's argument has been considered in full but not found convincing.

Therefore, the rejection of record is **maintained** for the reasons of record, as it applies to the amended claims. The rejection of record is incorporated by reference herein, as if reiterated in full.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3, 6, and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bandman et al. (US Patent 6,203,979 B1, reference of record).

The following New Grounds of Rejection are necessitated by Applicant's amendment to the claims, filed 11/20/2008.

The Bandman reference has been discussed supra.

Bandman did not explicitly teach the step of determining if the test compound has an effect on a symptom of the disease in an in vivo assay. However, given that Bandman taught administering the test compound to subjects for treating disease, it would have been obvious to one of ordinary skill in the art would determine whether the

test compound has an effect on a symptom of the disease before treating the subject with the test compound.

Given that the prior art goal was to treat subjects with diseases with the test compound that binds NPEPL1, it would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing such methods to determine whether the test compound has an effect on a symptom of the disease before treating the subject with the test compound.

The rationale to support a conclusion that the claims would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. screening for the test compound that binds NPEPL1 and using the test compound as a therapeutic agent for treating diseases) within his or her technical grasp. This leads to the anticipated success of determine whether the test compound has an effect on a symptom of the disease before treating the subject with the test compound. It is likely the process not of innovation but of ordinary skill and common sense.

Therefore, the invention, as a whole, was *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON WEN whose telephone number is (571)270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571)272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Wen/
Examiner, Art Unit 1644
March 9, 2009

/Phillip Gambel/
Primary Examiner
Technology Center 1600
Art Unit 1644
March 12, 2009